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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/385

A1

(11) International Publication Number: **WO 97/14415**

(43) International Publication Date: 24 April 1997 (24.04.97)

(21) International Application Number: PCT/AU96/00658

(22) International Filing Date: 18 October 1996 (18.10.96)

(30) Priority Data:
PN 6057 19 October 1995 (19.10.95) AU

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ANALGESIC IMMEDIATE AND CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION

(57) Abstract

The present invention relates to pharmaceutical compositions and is particularly concerned with pharmaceutical compositions containing N-methyl-D-aspartate (NMDA) receptor antagonists and their use in the treatment of pain. Accordingly, there is provided a pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form. The present invention further provides a method for the therapeutic or prophylactic treatment of pain in a human or animal subject, the method including administering to the subject, a composition in accordance with the present invention. The method of the invention may be used to treat chronic or acute pain. The composition of the invention may be used in the pre-emptive treatment of pain. The NMDA receptor antagonist may be selected from a morphinan such as dextromethorphan and dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of any of the foregoing.

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Analgesic immediate and controlled release pharmaceutical composition

The present invention relates to pharmaceutical compositions and is particularly concerned with pharmaceutical compositions containing N-methyl-D-aspartate (NMDA) receptor antagonists and their use in the treatment of pain.

The amino acid glutamate is an excitatory neurotransmitter that is an agonist at many post-synaptic terminals of the central nervous system. The glutamate receptor complex is termed the NMDA receptor and is a potential target for therapeutic drugs. This receptor incorporates an ion channel complex which is novel because it is gated by both dual ligand binding (glutamate and glycine) and membrane voltage. Because of the novel requirements for activation, it is believed that the NMDA receptor complex plays only a minor role in routine synaptic transmission. However, the receptor complex may be activated following repeated afferent stimuli as occurs during trauma such as surgery. Repeated stimuli cause a temporal summation of C-fibre-mediated responses of dorsal horn nociceptive neurones; this phenomenon, increased output to a constant input, is known as wind-up.

Studies indicate that activation of the NMDA receptor complex in the spinal dorsal horn leads to increased spontaneous neural discharge, expanded receptive fields and exaggerated responses to afferent input. These neural mechanisms may be expressed physically as hyperalgesia (increased pain sensation) and allodynia (pain arising from a stimulus that is not normally painful).

Opioids, through their ability to inhibit release of primary afferent neurotransmitters or to inhibit interneurons early in nociceptive pathways, initially reduce or block C-fibre inputs to the deeper dorsal horn nociceptive neurones. However, as the peripheral stimulation continues, wind-up breaks through the input inhibition and the neurons start to respond. Thus at moderate doses, opioids delay the onset of wind-up without inhibiting the process itself.

By contrast, NMDA receptor antagonists have no effect on the initial inputs to the cells but diminish or abolish wind-up and convert the potentiated response to a normal response.

We have found that a particularly effective composition for the administration of an NMDA receptor antagonist to diminish or abolish wind up is one providing both immediate release of an NMDA receptor antagonist and controlled or sustained release of an NMDA receptor antagonist.

NMDA antagonist receptors have also been indicated to be effective in the treatment of Huntington's disease, amyotrophic lateral sclerosis (ALS), AIDS-related dementia, Alzheimer's disease, schizophrenia, motoneurone diseases and CNS and brain injuries resulting from a number of causes including stroke, trauma and neurosurgery.

In accordance with one aspect of the present invention there is provided a pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form.

The same NMDA receptor antagonist may be used in both the immediate and controlled release forms or they may be different NMDA receptor antagonists.

The composition of the invention is suitable for the treatment of chronic or acute pain, for example to be administered pre-operatively.

Accordingly, the present invention further provides a method for the therapeutic or prophylactic treatment of pain in a human or animal subject, the method including administering to the subject, a composition in accordance with the pres nt invention. The m thod of the inv ntion may be us d to treat chronic or acute pain.

The composition of the invention may be used in the pre-emptive treatment of pain.

Preferably the NMDA receptor antagonist may be selected from a morphinan such as dextromethorphan and dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of any of the foregoing.

The formulation may include sufficient NMDA receptor antagonist to provide from about 1-5000 mg/day, typically 1-1000 mg/day and preferably about 100-800 mg/day of the active ingredient. The composition includes an NMDA receptor antagonist in an immediate release form in association with a NMDA receptor antagonist in a controlled release form. The composition may include an amount of NMDA receptor antagonist in the immediate release form of approximately 5% to 90% of the total NMDA receptor antagonist, preferably 10% to 60%. An immediate release NMDA receptor antagonist content of about 15% to 50% is particularly preferred. The controlled release form of the NMDA receptor antagonist may constitute the remainder of the active ingredients.

The composition of the invention may be in a form suitable for oral or rectal administration or for administration by transdermal, intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means.

The composition of the invention may or may not be in a single dosage form. Preferably the composition is in a single dose form.

The composition may be formulated as an oral dosage form such as a tablet, capsule, a liquid, powder, granule or suspension, an injectable solution, a suppository, implant or transdermal patch.

Preferably the NMDA receptor antagonist is dextromethorphan (DM) or a pharmaceutically acceptable salt thereof. Preferably the dextromethorphan is in the form of dextromethorphan hydrobromide.

The oral form of the pharmaceutical compositions of the invention may be selected from:

1) liquids, for example, suspensions, reconstitutable powders, elixirs, oils, solutions,or emulsions;

2) confectionery, for example, chewing gums, lozenges or candy bars;

3) powders, for example, drug powder, prilled material, coated actives or granulated materials;

4) capsules, for example, soft gelatin, hard gelatin containing, pellets, powders, tablets, granulates, liquids, or combinations of these; said capsules may or may not be coated;

5) tablets, for example, disintegrating, chewable effervescent, matrix, osmotic pumps, prepared by multi-layering, contain coated powders in tablets, tablets in tablets, pellets in tablets etc, said tablets may or may not be coated.

The oral pharmaceutical composition of the invention may be in the form of a "taste-masked" or "taste-neutral" form.

The method of manufacture, components and quantities of components used, depend on the particular pharmaceutical composition being considered.

A suitable immediate release (IR) form of the NMDA receptor antagonist may simply be particles of the antagonist or particles of the antagonist admixed with soluble components for example, sugars (eg sucrose, lactose, fructose, mannitol

etc.), polymers (eg polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulos , etc), surfactants (sodium lauryl sulphate, chremophor, tweens, spans, pluronics, and the like), insoluble components (microcrystalline cellulose, $Ca_3 (PO_4)_2$, talc, aerosol and the like), coating material (examples of suitable coating materials are polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids, etc.), dispersions in suitable material (examples are wax, polymers, pharmaceutically acceptable oils, soluble agents etc) or combinations of the above. These mixtures may be prepared by blending, mixing, dissolution and evaporation, or by using suspensions etc. These mixtures may be deposited on inert cores, wet massed and extruded, granulated, spray dried, etc. These mixtures or processed mixtures may be used in suspensions, filled into capsules, tabletted, filled into sachets, used in confectionery and so on.

The controlled release may be a sustained release or delayed/modified release.

A controlled-release dosage form as defined in US Pharmacopeia XXII includes extended release dosage forms which allow at least a twofold reduction in dosing frequency as compared to the drug presented as a conventional dosage form and delayed release dosage forms which release the drug at a time other than promptly after administration.

A core used herein the description contains the active ingredient and other carriers and excipients, fillers, stablising agents, binders, core seeds or colourants. The active may be present in amounts of approximately 0.1 to 95% by weight based on the weight of the total core element. Preferably the active is present in amounts of 10 to 80% by weight based on the weight of the total core element. The core may be 200 to 1700μ in diameter.

A pellet is a coated core, the coating being any suitable coating.

Preferably, the controlled release compon nt is a sustained (or extended) release form.

A suitable sustained release (SR) form of the NMDA receptor antagonist may b a matrix tablet composition. Suitable matrix forming materials are waxes (eg. carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, fatty alcohols), oils, hardened oils or fats (eg. hardened rapeseed oil, castor oil, beef tallow, palm oil, soya bean oil), polymers (eg. hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, polyethylene glycol) and other excipients known to those familiar with the art. Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, fillers, and excipients known to those familiar with the art. SR tablets may contain granulates, coated powders, pellets, or be multi-layered and the finished tablet may be coated or uncoated.

Suitable coating materials to prepare SR products are any pharmaceutically acceptable polymer such as ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars including lactose, sucrose, fructose and mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups. These polymers may be applied as solutions or latexes. Other barriers may be used such as waxes.

The coating composition may or may not be plasticised according to the prop rties of the coating blend such as the glass transition temperatur of the main compon nt or mixture of components or the solvent used for applying the coating compositions. Suitable plasticises can b added from 0 to 50% by weight

of the coating composition and at least on may b selected from diethyl phthalat , citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil and the like.

Cores containing active may be coated directly to produce a SR dose, or tablets or capsules containing active may be coated.

A suitable SR form of NMDA receptor antagonist may be an osmotic pump, or combinations of the above.

These IR or SR forms may be made by prilling, spray drying, pan coating, melt granulation, granulation, wurster coating, tangential coating, top spray, tabletting, extruding, coacervation and the like.

The particle sizes of the IR and SR components in the dosage form depends on the technology used. The particle sizes could range from submicron to 500 μm for powder technologies (mixtures, spray drying, dispersions etc), 5-1700 μm for coating technologies (wurster, top spray, bottom spray, spray drying, extrusion, layering etc), to 1-40mm for tabletting technologies.

The IR and SR forms of the NMDA receptor antagonist are then combined into a single dosage such that the amount of NMDA receptor antagonist in the composition of the invention is in the range of about 1 - 5000 mg typically, 1 mg to 1000 mg, and preferably 100 mg to 800 mg. The composition including an NMDA receptor antagonist in an immediate release form in association with a NMDA receptor antagonist in a controlled release form may include an amount of NMDA receptor antagonist in the immediate release form of approximately 5% to 90% of the composition of the invention, preferably 10% to 60%. An immediate release NMDA receptor antagonist content of about 15% to 50% is particularly preferred. The controlled release form of the NMDA rec ptor antagonist may constitute the r mainder of the active ingredient.

As a result th final composition provides an amount of NMDA r ceptor antagonist for immediate releas following administration and an additional amount of NMDA receptor antagonist for sustained release. The SR component is preferably aimed at reducing the dosage interval from 3 to 6 times daily to 1 or 2 times daily.

The composition of the invention may exhibit more than one peak in the plasma concentration/time curve in any one dosing interval depending on the particular NMDA receptor antagonist(s) used, the relative amounts of the IR and SR components, and the dissolution properties of the SR component.

The following non-limiting example illustrates the uses of the components listed above in producing a composition in accordance with the invention.

Where the composition of the invention is in the form of a pellet product, the pellets may be presented in a sachet, capsule or tablet. The non limiting example below describes pellets (particle sizes 200 - 1 700μm) in a capsule. All the quoted ranges are %w/w.

A plurality of elements containing the active ingredients (cores) are prepared by extrusion/marumerisation, or layering the active (or blend of active with other excipients) onto inert carriers by various processes. The cores themselves could be IR or SR depending on the materials and method of manufacture. The cores may contain the drug at the required potency according to the particular NMDA dose (mg), required size and presentation, and subsequent processes (coating etc.) The cores may contain drugs in the range 0.1-100% depending on the required dose, potency, manufacturing method, and properties.

An extruded core would typically include a carrier such as microcrystalline cellulose in the rang 5-99.9%, a bind r such as hydroxypropyl cellulose in the range 0-50%, a filler such as lactose in the range 0-50% and other excipients. An extruded core may only contain drug and binder.

An extruded core with SR properties would typically contain a swelling/gelling polymer such as hydroxypropyl cellulose in the range 0-50% or a hydrophobic material such as cetylalcohol in the range 10-90% with the drug. A layered core would contain an inert carrier such as a sugar sphere in the range 10-90% with a binder in the range 0.1-50 % with the drug. The core may or may not contain fillers, solubilisers and other additives. The binder may be chosen to achieve IR (hydroxypropyl cellulose, hydroxypropyl methyl cellulose etc), or SR (ethyl cellulose, cellulose acetate butyrate etc), or delayed/modified release (ie enteric binding materials such as hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate etc).

A portion of the final dosage form may be IR cores made by the above described processes. Alternatively the IR cores may be coated with a rapidly disintegrating or dissolving coat for aesthetic, handling, or stability purposes. Suitable materials are polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol, polymethacrylates containing free amino groups, each may be with or without plasticisers, and with or without an antitack agent or filler. An addition of about 3% of the weight of the core as coating material is generally regarded as providing a continuous coat for this size range.

The SR portion of the dose may be provided by a SR core as described above, a SR core which is further modified by overcoating, or an IR core which is modified by overcoating. The IR and SR NMDA receptor antagonist need not be the same active, nor are the IR or SR components of a dose themselves limited to just one active.

A typical coating composition for making the SR component would contain an insoluble matrix polymer in amounts approximately 15 - 85% by weight of the coating composition and a water soluble material in an amount of approximately 15 - 85% by weight of the coating composition . Optionally an enteric polymer in amounts from 0 to 100% by weight of the coating composition may be used or

included. Suitabl insoluble matrix polymers include ethyl cellulose, cellulose acetat butyrate, cellulos acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (eg lactose, sucrose, fructose, mannitol and the like), salts (eg. sodium chloride, potassium chloride and the like), organic acids (eg. fumaric acid, succinic acid, lactic acid, tartaric acid and the like) and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, polymethacrylates containing carboxyl groups, and the like.

The coating composition may or may not be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers can be added from 0 to 50% by weight of the coating composition and at least one may be selected from diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, castor oil and the like.

The coating composition may or may not include a filler. The filler may comprise 0 to approximately 200% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, polacrilin potassium, and the like.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. Where solutions are applied the solvent is pr sent in amounts from approximate by 25-99% by w ight pr ferably 85-97% by weight based on the total weight of dissolved solids. Suitable solv nts are wat r, lower alcohol, lower chlorinated hydrocarbons, ketones or mixtur s thereof.

Where latexes are applied, the solvent is present in amounts from approximately 25 - 97% by weight, preferably 60-97% based on th quantity of polymeric material in the latex. The solvent may be predominantly water.

A suitable tablet formulation may be of a swelling/gelling polymer such as L-hydroxypropyl cellulose admixed with a filler such as MCC and the drug. The tablet excipients may or may not be processed ie. spray dried together, prior to use in tabletting. The mixture may be compressed directly, or granulated prior to compression. Matrix tablets of this type often exhibit a rapid initial release until the polymers swell and gel, which induces SR for the remainder of the drug.

The quantity of IR and duration of SR can be varied by altering the quantities of the excipients used. If the IR component is not large enough, a quantity of drug can be included in a rapidly dissolving outer coat of polymers such as PEG or hydroxypropyl methyl cellulose. A typical matrix tablet would contain the swelling/gelling polymer in amounts from approximately 15 to 70% by weight based on the total weight of the tablet and filler in amounts from approximately 15 to 70% by weight based on the total weight of the tablet. Additional fillers may be included in amounts from approximately 0 - 60% by weight based on the total weight of the tablet. These may be soluble materials such as lactose, mannitol, sorbitol and the like, or insoluble materials such as tribasic calcium phosphate powdered cellulose or any of the various starches (corn, wheat, potato etc.) Additionally, the tablets may contain a lubricant in an amount from 0-8% by weight based on the total weight of the tablet. Lubricants may be selected from metal stearates, stearic acid, hydrogenated oils, such as soya bean oil or castor oil, sodium stearyl fumarate, polytetrafluoroethylene, talc and the like. The tablets may be coated for aesthetic, handling or stability purposes, or to increase the quantity of the IR portion of the drug. In this latter case the drug is dissolved or suspended in the coating solution and sprayed onto the tablets until the desired quantity of drug has b en added. Suitable coating materials include polyethylene glycol, hydroxypropyl methyl cellulose, hydroxypropyl c llulose, polyvinyl alcohol, polyvinylpyrrolidone, sugar, waxes, or mixtur s of these. The material may be

added to any desired thickness but weight gains in the range 1-20% are typical, preferably 2-10%, more preferably 2-5%. The coat may or may not be plasticised. A plasticiser may be present in amounts from about 0-50% by weight based on the total weight of the tablet of the coating material. Examples of plasticisers are diethyl phthalate, citrate esters, acetylated citrate esters, polyethylene glycol, glycerol, dibutylsebacate, acetylated monoglycerides, castor oil and the like).

The coating composition may include an antitack agent such as talc, kaolin, titanium dioxide, silicon dioxide, alumina, starch, polacrilin potassium, microcrystalline cellulose or the like).

The coating materials may be applied to the drug particles, processed drug particles (ie. cores, granules), finished tablets, or finished capsules.

The coating composition may or may not include a filler. The filler may comprise 0 to approximately 200% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, microcrystalline cellulose, polacrilin potassium.

The coat may contain other ingredients such as dyes and waxes.

The coat may be applied as a solution or suspension from aqueous or organic solvents solution concentration in equipment familiar to these skilled in the art. The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. Where solutions are applied the solvent is present in amounts from approximate by 25-99% by weight preferably 85-97% by weight based on the total weight of dissolved solids. Suitable solvents are water, go lower alcohols, lower chlorinated hydrocarbons, ketones, or mixtures thereof. Where latexes are applied, the solvent is present in amounts from approximately 25 - 97% by weight, preferably 60-97% based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

Alternatively the SR component of a tablet may be provided in the form of SR pellets and the IR component may be included in the body of the tablet. Such a tablet disintegrates to release the IR drug and the SR pellets. Pellets may be present in amounts from 1 - 60% by weight of the tablet, preferably 5 -50% more preferably 5 -40%. Suitable matrix materials for tablets of this type are microcrystalline cellulose, starches and the like.

The immediate release form of the NMDA receptor antagonist may be presented in a fast dissolving dosage form. The immediate release form may be in the form of a solid or molecular dispersion of the active within a polymer matrix. The polymer matrix may be selected from biologically acceptable polymer such as a cellulose ether, for example ethyl cellulose, or cellulose ester, for example cellulose acetate butyrate etc. The immediate release form may simply be particles of the antagonist or the antagonist deposited on a core containing the antagonist.

The composition of the invention, where it is in a tablet or like form, may include the two forms of the NMDA receptor antagonist as separate components, for example, in a multi-layer tablet, wherein one or more layer include the NMDA receptor antagonist in an immediate release form with one or more layers of the NMDA receptor antagonist in a controlled release form. Alternatively the composition of the invention may be in the form of a tablet wherein the immediate release forms the shell and the controlled release form constitutes the core.

Alternatively, the two forms of the NMDA receptor antagonist may be dispersed throughout the tablet.

The composition of the invention may be produced by providing a core containing the NMDA receptor antagonist controlled release component coated with an enteric or delayed release coating. The core can be in the form of beads compressed to a tablet. The coated core may then be compressed into tablets

along with a powder mixtur containing additional NMDA receptor antagonist or filled in combination with uncoated NMDA receptor antagonist into a capsule shell. As a result, the final composition provides an amount of NMDA receptor antagonist for immediate release following administration and an additional amount of NMDA receptor antagonist for controlled release.

The controlled release form of the NMDA receptor antagonist is such as to provide sustained release of the antagonist. Preferably the controlled or sustained release form provides a therapeutic effect over a period greater than about 6 hours. More preferably the sustained therapeutic effect is greater than about 8 hours. A sustained therapeutic effect period of 8 to 24 hours being especially preferred. The SR component of the controlled release composition is aimed at reducing the dosage interval from 3 to 6 times daily to 1 to 2 times daily.

The controlled release form of the antagonist may be coated beads or granules of the NMDA receptor antagonist. The coated antagonist may be combined with uncoated or lightly coated antagonist to provide a composition of the present invention. The term "lightly coated" as used in the description means a rapidly disintegrating coating for aesthetic, handling or stability purposes. These then may be filled into capsules or formed into tablets. Microencapsulation may also be used to produce the controlled release form of the NMDA receptor antagonist.

The coating or matrix material may be any suitable material. The coating or matrix material may be a polymer or a wax. The wax may be selected from any suitable wax or wax-like material including natural oil and fat and hardened oils such as hardened rapeseed oil, hardened castor oil, hardened beef tallow, palm oils and the like; waxes such as carnauba wax, bees wax, paraffin wax, ceresine wax, shellac wax or a fatty acid.

The present inv ntion also provides a kit including a plurality of unit dosage forms, in a contain r or the like, the container including indicia indicative of a

dosage regimen, at least one of the unit dosages being in th form of a pharmac utical composition in accordance with the present invention.

The kit may further include unit dosages which provide immediate and controlled release of one or more actives such as an NMDA receptor antagonist. The kit may also include instructions for use of the kit.

Throughout the claims and description of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers and steps.

The present invention will now be more fully described with reference to the accompanying example. It should be understood, however that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention as specified above.

FIGURES

Figure 1: Dissolution rate of Sustained Release Dextromethorphan capsules

EXAMPLE 1

A DEXTROMETHORPHAN DISSOLUTION PROFILE

BACKGROUND

Dextromethorphan (DM) is an NMDA recpetor which has been in clinical use for many years. Pharmacokinetic data suggest that after a normal 60mg dose the absorption of the drug is quite rapid, reaching maximum plasma levels in 1 to 2 hours. However, the bioavailability of the drug is quite low, probably because of extensive first-pass hepatic metabolism. Once absorbed, DM is converted in the body to a metabolite (dextrophan) which is reported to be pharmacologically active. Both the parent and the metabolite have short half-lives (2 to 4 hours).

Since DM and the active metabolite have short half-lives, a controlled release formulation will be useful to provide up to 24 hour delivery of this NMDA receptor antagonist from a single dose.

METHOD

a) PRODUCTION OF DEXTROMETHORPHAN CAPSULES

Dextromethorphan capsules were prepared according to the following and dissolution profiles were determined on the capsules.

(i) Granulating Dextromethorphan Solution

Ingredient	% (W/W)
Ethanol 96 PC/BP	95.0
Hydroxy Propyl Cellulose BP/NF	5.0

Ethanol 96 PC/BP was added to a container. To this, Hydroxy Propyl Cellulose BP/NF was added while shear stirring. The solution was left to stir until all of the polymer was dissolved.

(ii) Coating Solutions

Formulation 1

Ingredient	% (W/W)
Ethanol 96 PC/BP	95.0
Hydroxy Propyl Methyl Cellulose BP/USP 603	2.0
Ethyl Cellulose N50	3.0

Ethanol 96 PC/BP and Hydroxy Propyl Methyl Cellulose BP/USP 603 were shear stirred. After the HPMC had dissolved, Ethyl Cellulose N50 was shear stirred into the solution. The solution was shear stirred until the Ethyl Cellulose had completely dissolved.

Formulation 2

Ingredient	% (W/W)
Ethanol 96 PC/BP	93.43
Diethyl Phthalate BP/USP	0.65
Methacrylic Acid Copolymer NF, Type C Powder	1.05
Ethyl Cellulose N50	3.59
Poly Ethylene Glycol (6000) NF	1.28

The above ingredients were combined with stirring to produce Coating Formulation 2.

(iii) Dextromethorphan Cores

Dextromethorphan Cores Part 1

The cores containing dextromethorphan were produced in a fluid bed coater at the following conditions:

Inlet Air Temperature:	50°C
Air Flow:	80 m^3/hr

Two sets of dextromethorphan containing cores were produced; one with dextromethorphan potency of 57.75% and one with a potency of 80%. Both cores were made in a fluid bed coater with the ingredients listed below using standard methods known to those skilled in the art. The particle size range of the final cores was 710-1400 microns for the low potency cores and 1000-1700 microns for the high potency cores. In order that the desired capsule size would be used, the high potency cores were used in the next part of the process.

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	-	0.200
Dextromethorphan Granulating Solution	43.82	1.560
Dextromethorphan HBr	33.71	1.200
Sugar Spheres 30-35 Mesh	22.47	0.800

Theoretical Potency at the end of Dextromethorphan Core Part 1 is 57.75%.

Dextromethorphan Core Part 2

The cores containing dextromethorphan were produced in a fluid bed coated at the following operating conditions:

Inlet Air Temperature: 50°C

Air Flow: 80 m^3/hr

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	-	0.200
Dextromethorphan Granulating Solution	43.82	1.560
Dextromethorphan HBr	33.71	1.200
Dextromethorphan Cores Part 1	22.47	0.800

Theoretical potency at the end of Dextromethorphan Core Part 2 is 80%.

The final core will have the following composition.

Ingredient	% (W/W)
Dextromethorphan HBr	79.98
Hydroxy Propyl Cellulose BP/NF	5.20
Sugar Sph res (30-35) Mesh	14.82

(iv) Dextrom thorphan P ll ts

The high potency dextromethorphan cores were disp nsed with on_ of the coating formulations and talc in a fluid bed coater to produce the pellets. The process was run with the two different coating formulations and two different theoretical polymer coat weights (TPCW) were produced with Coating formulation 1. The conditions in the fluid bed coater are as follows:

Inlet Air Temperature:	50°C
Air Flow:	80 m^3/hr
Dew Point:	0°C

The pellets were produced by standard coating methods well known to those skilled in the art. The final pellets within the size range 1000-1700 microns were retained.

Aim Product for A6-048 A1 (8% Theoretical Polymer Coat Weight (TPCW)). A6-048 A1, A6-052 A2, and A6-048 A2 are batch numbers used to identify different pellet compositions.

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	-	0.2000
Coating Formulation 1	62.51	1.7400
Talc Purified Micronised BP/USP	1.56	0.0435
Dextromethorphan Cores	35.93	1.0000

Aim Product for A6-052 A2 (10% Theoretical Polymer Coat Weight (TPCW)

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	-	0.2000
Coating Formulation 2	67.80	2.2222
Talc Purified Micronised BP/USP	1.69	0.0555
Dextromethorphan Cores	30.51	1.0000

The resulting Dextromethorphan Pellets have an excipient breakdown as follows.

Dextromethorphan Pellet A6-052 A2 (10% TPCW)

Ingredient	% (W/W)
Dextromethorphan HBr	68.56
Hydroxy Propyl Cellulose BP/NF	4.46
Sugar Spheres (30-35) Mesh	12.70
Ethyl Cellulose N50	5.20
Diethyl Phthalate BP/USP	0.94
Methacrylic Acid Copolymer NF, Type C Powder	1.52
Poly Ethylene Glycol (6000) NF	1.86
Talc Purified Micronised BP/USP	4.76

Dextro Pellet A6-048 A1 (8% TPCW)

Ingredient	% (W/W)
Dextromethorphan HBr	70.75
Hydroxy Propyl Cellulose BP/NF	4.60
Sugar Spheres (30-35) Mesh	13.11
Hydroxy Propyl Methyl Cellulose BP/USP 603	3.08
Ethyl Cellulos N50	4.61
Talc Purified Micronised BP/USP	3.85

Dextro Pell t A6-048-A2 has a 10% TPCW with th sam xtract coating solution.

(v) Capsul

Capsules were filled by blending cores with pellets. Each size 0, natural / natural capsule contained 250 mg of dextromethorphan. The ratio of core ADS equivalent to pellet ADS equivalent was 25/75. This meant that 62.5 mg of dextromethorphan was contained in the immediate release cores, and 187.5 mg of dextromethorphan was contained in the controlled release pellets. The potencies of each of the cores and pellets was determined by UV assay.

b) MEASUREMENT OF DISSOLUTION OF DEXTROMETHORPHAN CAPSULES

Dissolution was measured using USPXXIII apparatus and method for dissolution <711>, apparatus 1. The analysis measures the UV absorbance of dextromethorphan at 278nm.

RESULTS

DISSOLUTION PROFILE OF DEXTROMETHORPHAN CAPSULES

Dissolution of the dextromethorphan capsules was measured according to the parameters above. The theoretical dissolution profile is compared with actual dissolution profile in Table 2 and shown in Figure 1. An aim dissolution profile was established with reference to the pharmacokinetic parameters, derived from the literature of immediate release dextromethorphan.

TABLE 2: AIM AND ACTUAL DISSOLUTION

	Aim		Actual		
Time (hours)	% Released	± 20% limit	A6-048 A1	A6-048 A2	A6-052 A2
0.5	27.5	22-33	25.8	24.9	26.7
1	30	24-36	28.0	26.5	27.8
2	35	28-42	33.3	29.5	31.5
4	45	36-54	43.8	36.3	42.2
6	55	44-66	55.2	44.4	53.2
8	65	52-78	66.8	53.3	64.1
12	85	68-100	87.9	71.8	82.0
16	100	>80	99.6	87.7	94.3

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

CLAIMS

1. A pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form.

2. A pharmaceutical composition according to claim 1 wherein the controlled release is sustained release or delayed/modified release.

3. A pharmaceutical composition according to claim 1 or 2 providing an NMDA receptor antagonist to a human or animal subject such that the NMDA receptor antagonist is in the range of from about 1 to 5000 mg.

4. A pharmaceutical composition according to claim 3 providing an NMDA receptor antagonist to a human or animal subject such that the NMDA receptor antagonist is in the range of from about 1 to 1000 mg.

5. A pharmaceutical composition according to claim 3 providing an NMDA receptor antagonist to a human or animal subject such that the NMDA receptor antagonist is in the range of from about 100 to 800 mg.

6. A pharmaceutical composition according to any one of claims 1-5 wherein an NMDA receptor antagonist in the immediate release form comprises 5% to 90% of the total weight of the NMDA receptor antagonist.

7. A pharmaceutical composition according to claim 6 wherein the NMDA receptor antagonist in the immediate release form comprises 10%-60% of the total weight of the NMDA receptor antagonist.

8. A pharmaceutical composition according to claim 6 or 7 wherein the NMDA receptor antagonist in the immediate release form comprises 15%-50% of the total weight of the NMDA receptor antagonist.

9. A pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject including an NMDA receptor antagonist in an immediate release form in a single dosage form combined with an NMDA receptor antagonist in a controlled released form.

10. A pharmaceutical composition according to claim 9 wherein the controlled release is sustained release or delayed/modified release.

11. A pharmaceutical according to claim 9 or 10 wherein the immediate release or sustained release form of the NMDA receptor antagonist are combined in a single dosage form such that the amount of NMDA receptor antagonist in the composition is in the range of about 1 mg to 5000 mg.

12. A pharmaceutical composition according to claim 11 wherein the amount of an NMDA receptor antagonist is in the range of 1 mg to 1000 mg.

13. A pharmaceutical composition according to claim 11 wherein the amount of NMDA receptor antagonist in the range of 100 mg to 600 mg.

14. A pharmaceutical composition according to any one of claims 9 to 13 wherein an NMDA receptor antagonist in the immediate release form comprises from 5 to 90% of the total weight of the NMDA receptor antagonist.

15. A pharmaceutical composition according to claim 14 wherein the NMDA receptor antagonist in the immediate release form comprises from 10 to 60% of the total weight of th NMDA receptor antagonist.

16. A pharmaceutical composition according to claim 14 wherein the NMDA receptor antagonist in th immediate release form comprises from 15 to 50% of the total weight of the NMDA receptor antagonist.

17. A pharmaceutical composition according to any one of claims 1 to 16 wherein a portion of the NMDA receptor antagonist is immediately released following administration and a portion is sustained released to provide therapeutic effect over a period of greater than 6 hours to provide a dosage interval of at least 1 to 2 times per day.

18. A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 8 to 24 hours.

19. A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 8 to 12 hours.

20. A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 12 to 24 hours.

21. A pharmaceutical composition according to any one of claims 17 to 20 which exhibits more than one peak in a plasma concentration/time curve in any one dosage interval.

22. A pharmaceutical composition according to any one of claims 1 to 21 wherein the NMDA receptor antagonist in the immediate release or controlled release form is the same or different.

23. A pharmaceutical composition according to any one of claims 1 to 22 wherein the immediate release or controlled release form are in a form selected from the group including active cores comprising active; tablets; multi-layered tablets; capsules containing active cores, either coated or uncoated; liquids;

powder; granules or p ll ts, either coated or uncoated; suspensions; an inj ctable solution; a suppository; implant; transdermal patch; or osmotic pump.

24. A pharmaceutical composition according to claim 23 wherein the immediate release and controlled release form of the NMDA receptor antagonist are separate components in a multi-layer tablet wherein one or more layers include the NMDA receptor antagonist in an immediate release form and one or more layers include the NMDA receptor antagonist in a controlled release form.

25. A pharmaceutical composition according to claim 23 wherein the immediate release and controlled release forms of the NMDA receptor antagonist are dispersed throughout a tablet.

26. A pharmaceutical composition according to claim 23 wherein the immediate release and controlled release form of the NMDA receptor antagonist are separate components in a capsule wherein one or more components include the NMDA receptor antagonist in an immediate release form and one or more components include the NMDA receptor antagonist in a controlled release form.

27. A pharmaceutical composition according to claim 26 wherein one or more of the components are active cores or pellets and wherein the active cores are uncoated or coated for immediate or controlled release of the active and wherein the pellets are coated for controlled release of the active.

28. A pharmaceutical composition according to claim 26 or 27 comprising a blend of cores and pellets wherein a ratio of cores to pellets is 25/75.

29. A pharmaceutical composition according to any one of claims 1 to 28 including dextromethorphan or a salt thereof in a dosage form wherein the dissolution rat in vitro of the dosag form, when m asured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH b tween 1.6 and 7.2) at 37°C is between 22% and 33% (by weight) dextromethorphan released after 0.5 hour,

between 24% and 36% (by weight) dextromethorphan released after 1 hour, between 28% and 42% (by weight) dextromethorphan released after 2 hours, between 36% and 54% (by weight) dextromethorphan released after 4 hours, between 44% and 66% (by weight) dextromethorphan released after 6 hours, between 52% and 78% (by weight) dextromethorphan released after 8 hours, between 68% and 100% (by weight) dextromethorphan released after 12 hours, and greater than 80% (by weight) dextromethorphan released after 16 hours.

30. A pharmaceutical composition according to any one of claims 1 to 29 wherein the NMDA receptor antagonist is a morphinan selected from the group including dextromethorphan and dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of any of the foregoing.

31. A pharmaceutical composition according to any one of claims 1 to 30 wherein the NMDA receptor antagonist is dextromethorphan (DM) or a pharmaceutically acceptable salt.

32. A pharmaceutical composition according to claim 31 wherein the NMDA receptor antagonist is dextromethorphan hydrobromide.

33. A pharmaceutical composition according to any one of claims 1 to 32 wherein the immediate release forms of the NMDA receptor antagonist are particles of the antagonist or particles of the antagonist admixed with soluble components selected from the group including sugars including sucrose, lactose, fructose, mannitol; polymers including polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose; surfactants including sodium lauryl sulphate, chremophor, tweens, spans, pluronics; insoluble components including microcrystalline cellulose, $Ca_3(PO_4)_2$, talc, aerosol; coating material including polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids; dispersins in

suitabl mat rial including wax, polym rs, pharmac utically acc ptable oils, solubl agents or combinations thereof.

34. A pharmaceutical composition according to any one of claims 1 to 33 wherein the controlled release form of the NMDA receptor antagonist is in a matrix composition selected from the group including waxes including carnauba, bees wax, paraffin wax, ceresine, shellac, fatty acids, fatty alcohols; oils, hardened oils or fats including hardened rapeseed oil, castor oil, beef tallow, palm oil, soya bean oil; insoluble matrix polymers including ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers; water soluble matrix materials including polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials including sugars including lactose, sucrose, fructose, mannitol, salts including sodium chloride, potassium chloride, organic acids including fumaric acid, succinic acid, lactic acid, tartaric acid and mixtures thereof.

35. A pharmaceutical composition according to claim 34 further including an enteric polymer selected from the group including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups or combinations thereof.

36. A pharmaceutical composition according to any one of claims 1 to 35 wherein the composition further includes a binder selected from the group including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose, cellulose acetate butyrate, or enteric binding materials such as hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate or combinations thereof.

37. A pharmaceutical composition according to any one of claims 1 to 36 wherein the imm diate release or controlled rel ase forms are coated with a pharmaceutically acceptable coating composition comprising ethyl cellulose,

cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptabl polymers, polyethyl ne glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars including lactose, sucrose, fructose and mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

38. A pharmaceutical composition according to claim 37 wherein the coating composition includes a plasticiser from 0 to 50% by weight selected from the group including silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, polacrilin potassium, or any combination thereof.

39. A pharmaceutical composition according to any one of claims 1 to 38 further including a filler comprising 0 to 200% w/w and selected from the group including silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, microcrystalline cellulose, polacrilin potassium, or any combination thereof.

40. A pharmaceutical composition according to any one of claims 1 to 39 further comprising a swelling/gelling polymer selected from the group including hydroxypropyl cellulose in the range 0-50% w/w or a hydrophobic material such as cetylalcohol in the range 10-90% w/w.

41. A pharmaceutical composition according to any one of claims 1 to 40 in a form suitable for oral or rectal administration or for administration by transdermal, intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means.

42. A method of preparing a pharmaceutical composition for the administration of an NMDA rec ptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form said method including:

providing a matrix or coated core containing an NMDA receptor antagonist to provide controlled release of a NMDA receptor antagonist;

providing a mixture containing a NMDA receptor antagonist to provide an immediate release of a NMDA receptor antagonist; and

combining the matrix or coated core with the mixture.

43. A method according to claim 42 wherein the matrix core is a matrix composition selected from the group including waxes including carnauba, bees wax, paraffin wax, ceresine, shellac, fatty acids, fatty alcohols; oils, hardened oils or fats including hardened rapeseed oil, castor oil, beef tallow, palm oil, soya bean oil; insoluble matrix polymers including ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers; water soluble matrix materials including polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials including sugars including lactose, sucrose, fructose, mannitol, salts including sodium chloride, potassium chloride, organic acids including fumaric acid, succinic acid, lactic acid, tartaric acid and mixtures thereof.

44. A method according to claim 42 wherein the coated core is a core of NMDA receptor antagonist coated with a pharmaceutically acceptable polymer including diffusion barrier polymers with or without porosity enhancers selected from the group including ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, polyethyl ne glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monom ric materials such as sugars including lactose, sucrose, fructose and

mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

45. A method according to claim 42 wherein the core and the mixture are combined and compressed into a tablet form and wherein the core and the mixture are dispersed throughout the tablet form.

46. A method according to claim 42 wherein the core and the mixture are combined and compressed into a tablet form such that the core and the mixture form a multilayer tablet form.

47. A method according to claim 42 wherein the core and the mixture are combined into a capsule.

48. A method for the therapeutic or prophylactic treatment of pain in a human or animal subject, the method including administering to the subject, a composition according to any one of claims 1 to 41.

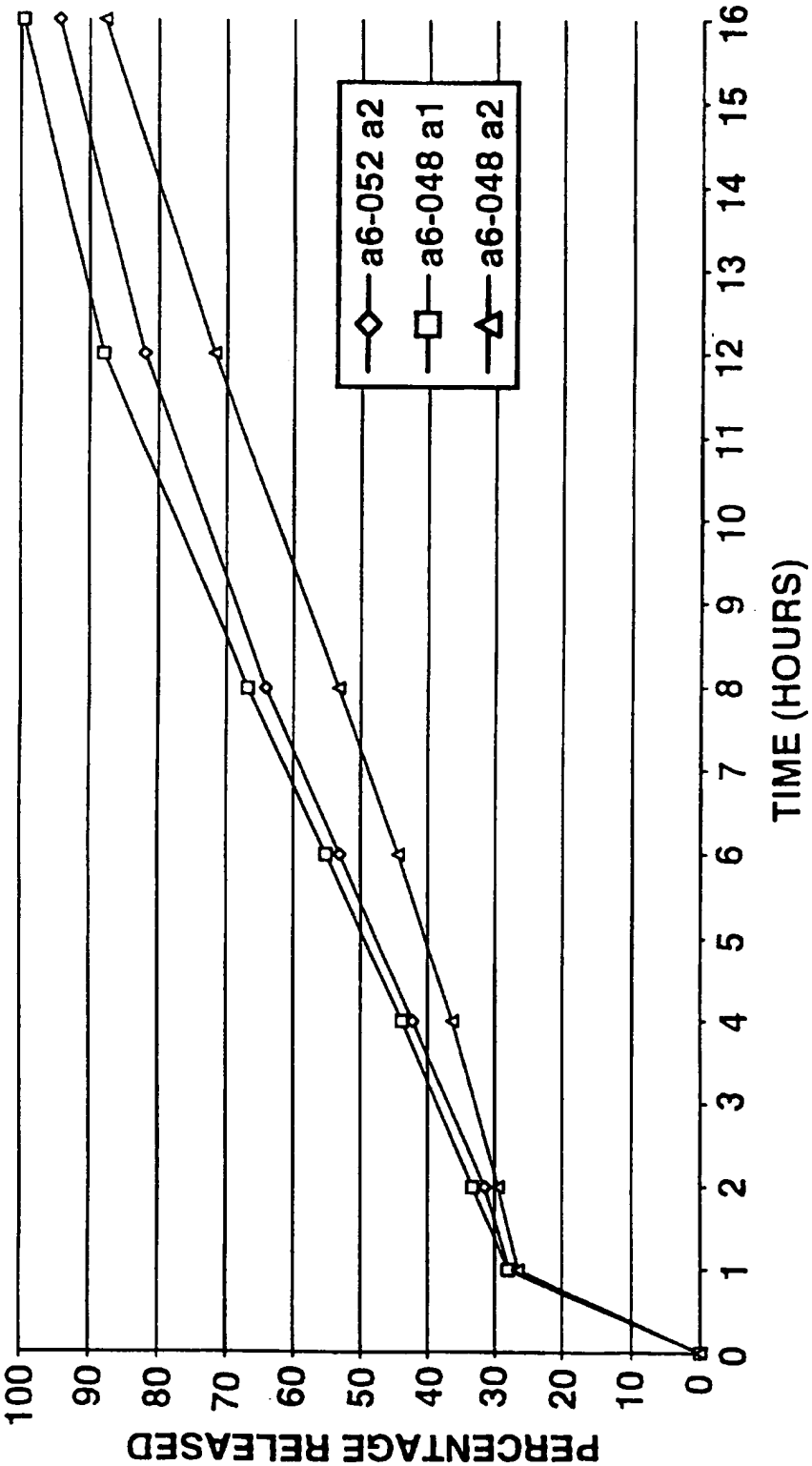
49. A method according to claim 48 for the treatment of chronic or acute pain.

50. A method according to claim 48 for the pre-emptive treatment of pain.

51. A method for the treatment of Huntington's disease amyotrophic lateral sclerosis (ALS), AIDS-related dementia, Alzheimer's disease, schizophrenia, motoneurone diseases and CNS and brain injuries resulting from a number of causes including trauma, stroke and neurosurgery in a human or animal subject, the method including administering to the subject, a composition according to any one of claims 1 to 41.

52. A kit including a plurality of unit dosage forms, in a container or the like, the container including indicia indicative of a dosage regimen, at least one of the unit dosages being in the form of a pharmaceutical composition according to any one of claims 1 to 41.

53. A kit according to claim 52 further including instructions and unit dosage forms providing immediate release and controlled release of NMDA receptor antagonist.


a6-052 a2
a6-048 a1
a6-048 a2
PERCENTAGE RELEASED
100
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80
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TIME (HOURS)
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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00658

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 31/385

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/385

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU:IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT, CA : (Dextromethorphan, dextrorphan,ketamine,amantadine,memantine eliprodil,ifenprodil,dizocilpine,remacemide,lamotrigine,riluzole,aptiganel,phencyclidine,flupirtine,celfotel,felbamate,spermine,spermidine,levemopamil, OR NMDA() receptor ()antagonist and (control()release or sustain:release)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US A 5238686 (EICHEL et al.) 24 August 1993 see table 1x-B col.13	1-53
X	US A 5156842 (MULLIGAN et al) 20 October 1992 see tables 6 and 8 in col. 9-10	1-53
X	US A 5084278 (MEHTA) 28 January 1992 see col. 4 line 63 - col.5 line 5	1-53

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 1996	8 JAN 1997
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer **K.F. PECK** Telephone No.: (06) 283 2263

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00658

C (Continuation) **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US A 4859462 (CHOW et al) 22 August 1989 see table 1 col.4	1-53
X	US A 4859461 (CHOW et al) 22 August 1989 see table 1 col.4	1-53
X	GB A 2189995 (ALZA CORPORATION) 11 November 1987 see whole document, esp. Example 13	1-53

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00658

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5238686	AU	70124/87	CA	1285482	DK	1537/87
		EP	239361	JP	62246513	NO	871243
		ZA	8702154	US	5238686		
US	5156842	CA	1314215	DK	3336/88	EP	295941
		JP	1016717	PH	24979	US	5156842
US	5084278						
US	4859461	AU	70989/87	CA	1283998	DK	3947/87
		EP	254811	FI	872582	IL	82223
		JP	63035527	NO	873031	NZ	219816
US	4859462	AU	72422/87	CA	1283497	DK	3948/87
		EP	254822	FI	872581	IL	82426
		JP	63035526	NO	873184	NZ	219925
		PH	23585	ZA	8703016	US	4859462
GB	2189995	US	4716496				

END OF ANNEX